(b) reacting said carboxylic acid and methane sulfonic acid in the solvent, and

(c) isolating the resulting solid product which comprises 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate.

~~14.~~ 13 *(once amended)* A process according to claim ~~11~~ 10 wherein the crystallization solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

Please add the following claims:

~~19.~~ 18 A process according to claim 1 wherein the methanesulfonate sesquihydrate is crystallised out of solution by cooling.

~~20.~~ 19 A process according to claim 1 wherein the resulting solid product is dried.

~~21.~~ 20 A process according to claim 1 wherein the resulting solid product is dried at 50-55 °C under vacuum.

~~22.~~ 21 A process according to claim ~~11~~ 10 wherein the methanesulfonate sesquihydrate is crystallised out of solution by cooling.

~~23.~~ 22 A process according to claim ~~11~~ 10 wherein the resulting solid product is dried.

~~24.~~ 23 A process according to claim ~~11~~ 10 wherein the resulting solid product is dried at 50-55 °C under vacuum.

REMARKS

Upon entry of this amendment, claims 1-3 and 5-24 will be pending in the application. Claim 4 is being canceled without prejudice or disclaimer. Claims 1, 5, 6, 8, 11, and 14 are being amended. The amendment to claims 8 and 14 correct a typographical error, in accordance with the inventive process which comprises a single crystallization step. Claims 1 and 11 are being amended to provide express antecedent basis for "crystallization solution" now recited in dependent claims 8 and 14, to recite preferred ratios of the cosolvent and water, and to clarify that the resulting isolated solid product comprises the claimed methanesulfonate sesquihydrate. Claim 11 is further amended, and claim 6 is amended, to clarify the ratio of carboxylic acid :

solvent. Support for these amendments is found in the as-filed specification and claims, including page 1, lines 23-24, page 2, lines 12-16 and lines 21-27 , and original claim 6. No new matter is being added. New dependent claims 19-24 have been added and find support in the as-filed specification at page 2, lines 22-23 and page 3, lines 19-20.

The present invention is based on Applicants' surprising discovery that 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate (also referred to herein as "gemifloxacin mesylate sesquihydrate") can be prepared directly from 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (also referred to herein as "gemifloxacin free base") and methanesulfonic acid, reacted in a solvent comprising a water miscible cosolvent and water. This discovery advantageously eliminates a step in the synthesis of the gemifloxacin mesylate sesquihydrate. See, e.g., page 1, lines 11-24 and page 2, lines 33-36 of the specification.

Response to Office Action

Objection to Drawing

The Office Action includes a Notice of Draftsperson's Patent Drawing Review (Form PTO 948). The Notice states that Figure 1 is objected to as allegedly having unacceptable left and bottom margins. Applicants will submit corrected drawings within the time period specified in the form PTO 948, that is, before expiration of the three-month shortened statutory period set in a Notice of Allowability (PTOL-37), should one be issued. Applicants point out, however, that the bottom margin appears to meet the requirements of 37 CFR 1.84(g).

Rejections under 35 USC 103(a)

Claims 4-16 are rejected under 35 USC 103(a) as being allegedly unpatentable over Hong et al., US 5,776,944 (hereinafter "Hong").

The Examiner states that Hong discloses methods for making the instant sesquihydrate compound, which is said to be a preferred compound (citing columns 8 and 9, and particularly column 8, lines 39-43).

The Examiner also notes that the reference discloses a method of making the instant hydrates at column 14, line 48 to column 15, line 10. The Examiner notes the reference disclosure that "the different hydrates may be prepared merely by changing

the recrystallization conditions" (column 15, lines 5-10), which immediately follows the instructions for preparing the methane sulfonic acid salt (referencing column 14, line 48 to column 15, line 5). The Examiner posits that the disclosed steps involve mixing the free naphthyridinone and methane sulfonic acid, and that preferred solvents are dichloromethane, trichloromethane, methanol, ethanol, propanol and water. The Examiner further posits that the reference provides motivation to use mixtures of solvents, by way of the above referenced statement at column 15, lines 5-10.

Claims 1-16 are rejected under 35 USC 103(a) as being allegedly unpatentable over Hong, in view of Handanyan, et al., WO 96/39406 (hereinafter "Handanyan").

The Examiner relies on Hong as discussed above. Handanyan is relied upon as disclosing a method of making a hydrated methane sulfonic acid salt of a similar naphthyridinone carboxylic acid, by mixing the reactants in a mixture of water and THF. The Examiner concludes that one having ordinary skill in the art would have been motivated by Hong, and the obvious need to have water present, to use a mixture of water with one of the water miscible solvents disclosed by Hong (said to be the lower alkanols disclosed therein).

Applicants respectfully traverse the rejections under 35 USC 103.

The Examiner relies on the disclosure appearing at column 14, line 48 to column 15, line 10 of Hong as making obvious claims 3-16. As further discussed below, this disclosure would be understood by those skilled in the art to teach a process requiring two crystallization steps to prepare the gemifloxacin methanesulfonate hydrates, that is, a 1st crystallization step to form the mesylate anhydrate, followed by a 2nd, recrystallization step to form a mesylate hydrate. This differs from Applicants' claimed process, which does not utilize a recrystallization step.

That is, from column 14, line 48 to column 15, line 5, Hong describes making the gemifloxacin methanesulfonate salt from the free base and methanesulfonic acid, and forming the mesylate into a solid. An example of this process is given in Example 204 (wherein the solvent is dichloromethane and ethanol), which is disclosed as resulting in formation of an anhydride (i.e., an anhydrate). See, for example, mention of the "anhydride prepared in Example 204" in column 97, lines 39-40 and 43-44 (Example 206), column 100, lines 53-54, column 101, lines 17-18, and column 102, lines 17 and 37-38 of Hong.

In column 15, lines 6-10, Hong describes making "hydrates of the methanesulfonate of the present invention". Column 15, lines 9-10 state that "the different hydrates may be prepared merely by changing the recrystallisation conditions." These passages are clearly teaching formation of the hydrates by recrystallising the solid mesylate salt, which is formed in a 1st step that is described immediately beforehand in column 14, line 48 to column 15, line 5. An example of this process is described in Example 206 (wherein a water:acetone or water:ethanol recrystallisation of the solid anhydrate produces the n= 1.5 hydrate).

Clearly therefore, columns 14 and 15, and Examples 204 and 206 of Hong disclose a process having two crystallization steps, i.e., a 1st, solid formation step and a 2nd, recrystallisation step, to prepare the hydrates starting from the free base. Hong does not teach or suggest reacting the free base and methane sulfonic acid in a solvent to directly form mesylate sesquihydrate from a crystallization solution, as required by Applicants' claims.

Also, as implicitly acknowledged in the Office Action, neither the list of solvents at column 14, lines 57-61, nor Example 204 teach or suggest reacting the free base with methane sulfonic acid in a mixture of a water miscible cosolvent and water, as required by Applicants' claims.

Further, it would not have been obvious to one having ordinary skill in the art, having read Hong's process at columns 14-15 or Examples 204 and 206, that mesylate sesquihydrate could be formed directly from the reaction of gemifloxacin free base and methane sulfonic acid in a water miscible cosolvent and water as required by Applicants' claims. Rather, these disclosures in Hong teach away from Applicants' claims, because they teach that two steps are required to form the mesylate sesquihydrate from gemifloxacin free base.

Contrary to the Examiner's opinion, the large list of solvents in Hong column 14, lines 58-61 does not make the present claims obvious, as these solvents are implicitly disclosed for use in making the mesylate anhydrate and not the mesylate sesquihydrate. As discussed above, the disclosures of column 14, line 48 to column 15, lines 5-10 teach a process comprising two crystallization steps for preparing the reference hydrates. The column 15, lines 5-10 disclosure of "changing the recrystallisation conditions" in the 2nd step does not provide any motivation in the 1st step to form the mesylate sesquihydrate directly from the free base and methane sulfonic acid reacted in solvent comprising water and a water-miscible cosolvent, e.g.,

water and methanol, ethanol or propanol (cf. column 14 line 61). One having ordinary skill in the art would simply ignore column 15, lines 5-10 when determining what solvents to use to react the free base with methane sulfonic acid in the 1st step taught by Hong.

Handanyan discloses preparation of a crystalline mesylate from a different napthiridine-3-carboxylic acid and methane sulfonic acid (see Preparation A of WO 96/39406, pages 4-5). This disclosure is not predictive of crystal formation, no less crystals of a particular form, were the same process used with gemifloxacin free base and methane sulfonic acid. It is well known that processes suitable for making the crystal form of one compound are not predictably suitable for making a similar crystal form of a second compound. Therefore, it would not have been obvious to combine the teachings of Handanyan, relating to a different free base, with the teachings of Hong, no less to arrive at the invention presently claimed.

Furthermore, Handanyan's Preparation A (using the carboxylic acid, methane sulfonic acid, and water/THF), suggests formation of an anhydrate. For example, at page 4, lines 29-30, Handanyan states that the "residual water content of the crystals was below 0.2%", and at page 5, lines 9-13 that this methanesulfonate crystal form "can pick up water from the atmosphere and form a monohydrate". Even assuming *arguendo* that one having ordinary skill in the art would combine the teachings of Handanyan with those of Hong, Handanyan would further teach away from formation of a sesquihydrate, as required by the present invention.

The Applicants respectfully submit that the Examiner's rejections under 35 U.S.C. §103(a) over Hong, and further in view of Handanyan, have been overcome in view of the comments herein as they relate to the pending, amended and new claims. The Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicants respectfully submit that they have addressed and overcome all issues raised by the Examiner.

The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

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Marked up version of amendments

to claims 1, 5, 6, 8, 11 and 14, made May 8, 2002

1.(*once amended)* A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises:
(a) forming a crystallization solution comprising 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid, and a solvent comprising at least one least one water miscible cosolvent and water, wherein the ratio of water miscible cosolvent : water is in the range of 2:1 to 1:2 v/v,
(b) reacting said carboxylic acid and methane sulfonic acid in the solvent [7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one least one water miscible cosolvent and water] , and
(c) isolating the resulting solid product which comprises 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate.

5.(*once amended*) A process according to claim [4] 1 wherein the ratio of water miscible cosolvent : water is 2:1 v/v.

6.(*twice amended*) A process according to claim 1 wherein the ratio of 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is [up to] 1:100 w/v or more.

8.(*twice amended*) A process according to claim 1 wherein the [recrystallisation] crystallization solution is seeded with 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

11.(*once amended*) A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises:

(a) forming a crystallization solution comprising 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid, and a solvent comprising at least one least one C_{1-4} alcohol and water, wherein the ratio of C_{1-4} alcohol : water is in the range of 2:1 to 1:2 v/v, the ratio of said carboxylic acid to said solvent is 1:100 w/v or more, and from 0.7 to 1.5 mole equivalents of the methanesulfonic acid is used,

(b) reacting said carboxylic acid and methane sulfonic acid in the solvent [7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in solution with a solvent comprising at least one C_{1-4} alcohol and water, wherein from 0.7 to 1.5 mole equivalents of methanesulfonic acid is used, the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v , and the ratio of C_{1-4} alcohol : water is in the range 10:1 to 1:2 v/v] , and

(c) [(b)] isolating the resulting solid product which comprises 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate.

14.(*once amended*) A process according to claim 11 wherein the [recrystallisation] crystallization solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.